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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,374	03/10/2004	Jeffrey O. Phillips	04242350	4467

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EXAMINER	
CHANG, CELIA C	
ART UNIT	**PAPER NUMBER**
1625	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/797,374	PHILLIPS, JEFFREY O.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *151-154,156-159,163,165-170,172-178,180 and 182-236* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *151-154,156-159,163,165-170,172-178,180 and 182-236* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of group V, omeprazole and sodium bicarbonate in the reply filed on Oct. 13, 2006 is acknowledged.

Claims 1-150, 155, 160-162, 164, 171, 179, 181 have been canceled. Claims 151-154, 156-159, 163, 165-170, 172-178, 180, 182-236 as currently amended are pending.

2. Claims 151-154, 156-159, 163, 165-170, 172-178, 180, 182-236 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to "an orally deliverable pharmaceutical composition" comprising a "therapeutically effective" amount of omeprazole and sodium bicarbonate which will give a plasma concentration of omeprazole at 0.1 μg/ml; at about 30 minutes and the composition is of a solid dosage unit. It is not understood what is the product being claimed.

It is noted that on page 26, the "effective amount" is defined as the amount to elicit a pharmacologic or therapeutic effect. Nowhere in the specification did the "therapeutically effective" amount and the amount of a unit dosage "unit" be identified being the same of identical. One can administered a single unit dosage which contains a "therapeutically effective" amount thus achieve therapy or one can administered multiple unit dosage to make a "therapeutically effective" amount. While the method of treatment is the same therapeutic dosage, the compositions of the two scenarios are completely different. Especially, the dependent claims such as claim 156 has the limit of 1000 mg omeprazole, while a method of administering 1000 mg with five units of 200 mg per capsule can be achieved, a 1000 mg omeprazole "unit dosage" must have antecedent basis as well as how such unit dosage product can be made. Without description to such a product, the specification lacks sufficient descriptive support to the claims.

3. Claims 151-154, 156-159, 163, 165-170, 172-178, 180, 182-236 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claims are drawn to compositions which upon administering to a subject, will achieve a plasma concentration of omeprazole at 0.1 μg/ml; at about 30 minutes. Such a scope is highly unpredictable.

The state of the art and predictability

Serum concentration of omeprazole has been well established to depend on many parameters of determination.

Initially, it is noted that the "subject" of the claims are intended for human as well as animals. There is no description or uniformity as to the plasma concentration and dosage relationship in species variation. Nowhere in the specification or prior art that all animals have analogous physiology and would respond in similar manner when a give dose is administered. Birds (see CA 114:39637) normally have drastically different physiology from mammals.

Second, it is conventionally known that the condition wherein omeprazole is in a composition determines the rate of absorption thus plasma concentration. There is no description in the specification that enteric coated or uncoated omeprazole will operate in similar manner in the instant composition while prior art indicated enteric coated preparation gives highly unpredictable results (see CA 101:183381).

Third, it is conventionally known that the absorption rate/plasma concentration is highly unpredictable based on the "subject" being given the first dose or repeated dose (see CA

110:185703), thus, plasma concentration does not reflect the requirement of the product but is a result of the condition of the subject.

Fourth, the carrier of the drug contributes to the overall plasma concentration, the same carrier does not offer any predicable result of its effect on the drugs' bioavailability (see Sharma et al.) while the claims are drawn to open and no limitation with respect to carrier.

Fifth, the site of administration determines the overall plasma concentration (see Phillips et al.). On the same oral administration, through the gastric lumen or by-pass the gastric lumen i.e. a duodenal or jejunal administration gives different plasma concentration.

Therefore, in absence of defined "subject"; in absence of defined preparation of omeprazole; in absence of frequency/order of dosing; in absence of carrier; in absence of site of release after oral administration; the "plasma" concentration provided no *predictable correlation reflects the product it is administered.*

The amount of guidance and working examples

In the specification, on page 92, two 20 mg omeprazole capsules were administered together with 20 ml 8.4% sodium bicarbonate. On page 103, the subjects were give 40 mg powder together with 1 antiacid tablet to chew in the mouth, in pre-mixed suspension or co-administered with sodium bicarbonate. There is no description or enabling information on the "plasma concentration" as to a single solid unit that will achieve the required plasma C_{max}. Please note that the claims are drawn to "composition" which will give a plasma concentration of omeprazole at 0.1 μg/ml; at about 30 minutes after oral administration.

Further, there is insufficient description or enablement to the scope of claim 191 wherein any and all "enantiomer, isomer, tautomer, prodrug, free base or salt" of omeprazole can function in the same way in achieving identical plasma level/bioavailability as the omeprazole free base (Prilosec)as disclosed in the specification. Salts, isomers etc. of a known compound ordinarily have different physical properties for which no factual evidence was provided in the specification that such variation will be operable to achieve the C_{max} when given to subjects.

In view of the high unpredictability and the complex physiology in absorption and distribution of a given dose of drug, the lack of sufficient description and enablement has been clearly noted. While the plasma concentration of a drug can be measure upon given a cumulative dose with specific carrier, in a specific subject, under specific conditions of administration, such process does not provide enablement for a single solid unit that will give a plasma concentration of omeprazole at 0.1 μg/ml; at about 30 minutes *unless such product is in possession and demonstrated by factual evidence*.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 151-154, 156-159, 163, 165-170, 172, 175 are rejected under 35 U.S.C. 102(b) as being anticipated by Depui et al. WO 97/25066, JP 05-255088 supplemented with Horowitz (all cited on 1449).

Depui (p. 29, example 4) or Jp'088 (p. 5 tables 0018) disclosed composition anticipated the claims with the dosage and base combination. The limitation of serum level within 30 min is the innate nature of such composition as evidenced by Horotwitz (see page 792, col. 2, wherein after the oral administration of 90 mg omeprazole with 300 ml 160 mmol/l sodium bicarbonate, corresponding to 0.53 meq/mg omeprazole i.e. the claimed range, the medium time to reach the peak plasma concentration C mas-11.3±1.4 μm/l or 3.8 μg/ml is 30 min). Therefore, anticipation was found.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 151-154, 156-159, 163, 165-170, 172-178, 180, 182-236 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chavkin (U.S. Patent No. 4,613,497) in view of Junggren et al. (U.S. Patent No. 4,508,905) or Depui et al. WO 97/25066, JP 05-255088 supplemented with Horowitz further in view of Parachini, *Two New Drug Treatments Offer Hope to Ulcer Sufferers*, Los Angeles Times, Los Angeles, CA. Aug 30, 1988, pg 1 and Waring,

Questins and Answers about Medications and GERD, DIGESTIVE HEALTHCARE OF GEORGIA; available at: http://www.aboutgerd.org/MedQA.html.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Chavkin teaches using omeprazole as a gastric acid secretion inhibitor. Junggren et al. provide an antiacid tablet comprising bicarbonate and a phosphate (potassium bicarbonate and dicalcium phosphate dihydrate). See column 4, Example V. Both the PPI and the bicarbonate/phosphate combination are disclosed for treating acid-caused gastrointestinal disorders. Depui et al. disclosed that omeprazole can be combined with sodium bicarbonate in one composition JP 05-255088 disclosed that omeprazole can be coprecipitated with alumina hydroxide and sodium bicarbonate to form one composition. The instant claims are drawn to combined composition of omeprazole and sodium bicarbonate i.e. an antiacid composition for treating acid-caused gastrointestinal disorders.

Ascertainment of the Difference Between the Prior Art and the Claims (MPEP §2141.02)

The instant claims differ from the prior art by requiring both a PPI and sodium hydrogencarbonate in one solid formulation and to achieve a specific plasma level of omeprazole at about 30 min.

Motivation & Prima Facie Obviousness-Rationale (MPEP §§2142-2143)

It is conventional knowledge that both PPI and antiacid compositions are for the purpose of reducing gastric acid in acid reflux disorders. It is normally not patentable to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is to be used for the very same purpose. In re Kerkhover 205 USPQ 1069, Ex parte quadranti 25 USPQ2d 1071, Ex parte the NutrSweet Co., 19 USPQ2d 1586.

In the instant case, the two composition each conventionally known for the same function have been well delineated in the art. Motivation for the combination is explicitly suggested by Waring (*Questins and Answers about Medications and GERD*, DIGESTIVE HEALTHCARE OF GEORGIA; available at: http://www.aboutgerd.org/MedQA.html) who shows that it is a well-known procedure to take an antacid with a PPI and explains that over the counter antacids provide immediate relief from heartburn because they act quickly to neutralize stomach acid. "It

is fine to take these medications in combination." See page 3, fifth paragraph. Further, Parachini, (*Two New Drug Treatments Offer Hope to Ulcer Sufferers*, Los Angeles Times, Los Angeles, CA. Aug 30, 1988, pg 1) explained that PPIs must be absorbed in the gastrointestinal tract before they are effective and therefore do not immediate treat symptoms, therefore, Parachini **suggests** that an effective product "would be to "incorporate conventional [antacids] already on the market with a chewable or fizzy form of cimetidine (PPI)." Further, the Horowitz reference evidenced that a combination administration of omeprazole and antiacid sodium bicarbonate would provide the C_{max} at the time as required by the claims. The combination composition is prima facie obvious regardless of whether the skilled artisan knows of the stabilizing effect of antacids on preventing PPI degradation or what plasma concentration it may provide. Horowitz further provided evidence that the plasma level would flow naturally with such combination composition.

Applicant's attention is further drawn to the whole references of '497, '905, '066, '088 wherein general description on the variation of other carrier such as adjuvants, diluents, colorants etc. are conventional variations for an oral composition.

6. No claims allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie, Ph. D., can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Dec. 18, 2006

Celia Chang
Primary Examiner
Art Unit 1625